

REMARKS

Prior to this amendment claims 5, 9-16, 19-23, 26 and 30-34 were pending. Claims 5, 22, 26, 32 and 33 have been amended for technical clarity. Support for claim amendments can be found at page 6, lines 7-10 and 24-32, and page 7, lines 7-13 of the specification. In addition, submitted herein are new claims 35-38. Support is found in claim 22. No new matter is being added by way of this amendment.

The claim amendments are presented in a revised format per the USPTO's announcement 'Amendments in a Revised Format Now Permitted', signed 31 January 2002, and accordingly do not conform to the current reading of 37 C.F.R. §1.121, which Applicants understand has been waived. Accordingly, a complete listing of all claims that are, or were in the application, along with an appropriate status identifier, is provided above in the section entitled "Amendments to the Claims".

In addition, a proposed response was submitted on May 2, 2003, and a follow-up discussion with the Examiner indicated a favorable reaction.

Claim rejections based under 35 U.S.C. § 112, second paragraph

Claim 22 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 22 is rejected as vague and indefinite over the term " wherein said target sequence is attached to said support by a method selected from the group consisting of labeling said target sequence with a functional attachment moiety that binds said support" because the Examiner states that this phrase is a process for labeling and is not an attachment method. Without necessarily agreeing with the propriety of the rejection, Applicants have amended claim 22 for technical clarity. The above phrase has been amended to now read "attaching said target sequence with a functional moiety capable of binding to said support and interacting said functional moiety with said support".

Claim 22 is rejected as vague and indefinite in view of the phrase "absorption of said target sequence on a charged support" because it is unclear whether " a charged support" and "said support" in the claim represents the same thing or not. Without necessarily agreeing with

the propriety of the rejection, Applicants have amended claim 22 for technical clarity. The above phrase has been amended to now read “absorption of said target sequence on said support wherein said support comprises charged groups”. Applicants respectfully request the withdrawal of the rejection.

Claim rejections based under 35 U.S.C § 102 (e)

Claims 5, 13 and 32 are rejected as being anticipated by Barany et al. (U.S. Patent No. 6,027,889, filed on May 28, 1997). Applicants respectfully traverse.

Barany et al. is directed to detecting nucleic acid sequence differences using coupled ligase detection reaction (hereinafter referred to as LDR) and polymerase chain reaction (hereinafter referred to as PCR). Barany et al. is directed to either a) LDR coupled to PCR; b) primary PCR coupled to secondary PCR coupled to LDR; or c) primary PCR coupled to secondary PCR where oligonucleotides from an early phase of each process contain sequences which may be used by oligonucleotides from a later phase of the process.

It appears that the Examiner’s position is that Barany teaches LDR probes and that: (1) the first probe and second probe was considered as first and second ligation probe as recited in claims 5 and 32; (2) since the claims did not require that the adaptor sequence was different from UUP or DUP, 5’upstream primer-specific portion in the first and 3’ downstream primer-specific portion in the second probe were considered as UUP and DUP or an adaptor sequence as recited in claims 5 and 32 wherein the adaptor sequence was considered to be identical to UUP or DUP. (see p. 5 of the Office Action). The Examiner submits that Barany anticipates the present claims because the Examiner is reading the 5’ upstream primer-specific portion in the first probe as the UUP and 3’ downstream primer-specific portion in the second probe as the DUP; and either one could also be an adapter sequence. The Examiner appears to do this because the claims allegedly did not require that the adapter sequence and any of the UUP or DUP were different.

Applicants maintain that Barany does not anticipate the claims for the reasons made of record. Nevertheless, in order to further prosecution of this application, Applicants have amended the claims for technical clarity. As a result of this amendment, Applicants submit that the claims clearly recite that the adapters are distinct from the UUP or DUP, as being different portions of the recited probes.

Thus, each and every element of the claims as amended is not present in the prior art. Barany et al. does not teach or suggest methods that include hybridization of probes to a target, wherein the probes collectively include a) a first portion comprising an upstream universal

priming site (UUP); b) a second portion comprising a first target-specific sequence and an interrogation position that is complementary to said detection position; c) a third portion comprising a downstream universal priming site (DUP); d) a fourth portion comprising a second target-specific sequence; and e) a fifth portion comprising an adapter sequence contained on at least one of said first and second ligation probes.

Therefore Barany et al. does not anticipate the claims of the present invention. Accordingly the rejection is moot. Applicants respectfully request the withdrawal of the rejection.

Claims rejections based under 35 U.S.C. § 103(a)

Claims 14-16 and 34 are rejected under 35 U.S.C 103(a) as being unpatentable over Barany et al. (1997) as applied to claims 5, 13, and 32 above, and further in view of Walt et al., (U.S. Patent No. 6,327,410 B1, filed on September 11, 1998). Applicants respectfully traverse.

Barany et al. is discussed above and the arguments are incorporated at this point by reference. As set forth above, Barany et al. does not teach or suggest methods that include hybridization of probes to a target, wherein the probes collectively include five portions as recited herein.

Walt et al. is directed to microsphere-based chemistry system and method for making the same in which microspheres or particles carrying bioactive agents may be combined randomly or in ordered fashion and dispersed on a substrate to form an array while maintaining the ability to identify the location of bioactive agents and particles within the array using an optically interrogatable, optical signature encoding scheme. Walt et al. is silent with respect to adapter sequences. Walt et al. is also silent with respect to the hybridization of ligation probes to a target sequence with subsequent ligation and amplification of ligation probes. Walt is also silent with respect to hybridization of probes to a target, wherein the probes collectively include five portions as recited herein.

To establish a *prima facie* case of obviousness, several criteria must be established. There must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. In addition, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *In re Vaeck*, 947 F2d 488, 20 USPQ2d 1438 (Fed. Cir.

1991).

Applicants submit that the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F 2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990).

As stated above Barany et al. does not teach or suggest methods that include hybridization of ligation probes to a target, wherein the probes collectively include five portions as recited herein.

Furthermore, Walt et al. does not cure the deficiencies of Barany et al. Walt et al. is directed to microsphere-based chemistry system and method for making the same in which microspheres or particles carrying bioactive agents may be combined randomly or in ordered fashion and dispersed on a substrate to form an array while maintaining the ability to identify the location of bioactive agents and particles within the array using an optically interrogatable, optical signature encoding scheme. Walt et al. is silent with respect to adapter sequences. Walt et al. is also silent with respect to the hybridization of ligation probes to a target sequence with subsequent ligation and amplification of ligation probes.

Therefore, the cited references taken alone or in combination do not teach or suggest all of the elements of the claimed invention.

In addition, one of ordinary skill in the art would not have been motivated to modify or combine Walt and Barany to reach the claims of the present invention because, 1) as stated above there is no teaching or suggestion in either reference of modifying either reference or combining them to reach the claims of the present invention of method of determining the identification of a nucleotide at a detection position in a target through the use of ligation probes wherein the ligation probes collectively comprise the five portions as cited herein (which none of the cited references teach or suggest) and capturing the ligated probes on an array of capture probes where the array further comprises first and second subpopulations of microspheres and a substrate comprising discrete sites (claim 14), where discrete sites are wells (claim 15) and where the substrate comprises a fiber optic bundle (claim 16) or where the substrate comprises discrete wells and the substrate further comprises a fiber optic bundle (claim 34). Therefore, in addition to the fact that the cited references taken alone or in combination do not teach or suggest all of the elements of the claimed invention, there is also lacking any motivation to modify or

combine reference teachings to reach the claimed invention. Accordingly, the rejection is improper. Applicants respectfully request the withdrawal of the rejection.

Claims 10, 13, 19-22, 26, 31 and 33 are rejected under 35 U.S.C § 103(a)) as being unpatentable over Zhang et al., (U.S. Patent No. 5,876,924, filed July 31, 1996) in view of Barany et al., (1997).

Barany et al. is discussed above and the arguments above are incorporated at this point by reference.

In contrast, claims 5, 26 and 32, from which all other claims depend are directed to a method of determining the identification of a nucleotide at a detection position in a target sequence comprising steps of a) hybridizing probes to a target, wherein the probes include the five portions recited herein; b) amplifying the ligation product; c) contacting the amplicons with an array of capture probes and then d) detecting the nucleotide at the detection position.

However, as set forth above, Barany et al does not teach or suggest hybridization of probes to a target, wherein the probes include the five portions cited herein.

Furthermore, Zhang et al. do not cure the deficiencies of Barany et al. Zhang et al. is directed to methods for detecting nucleic acids in a sample involving hybridization of capture/amplification and amplification probes in the presence of paramagnetic beads coated with a ligand binding moiety with subsequent ligation of the probes. Alternatively, the methods are also directed to the use of separate capture and amplification probes to form full length or circular probes which may be detected directly or amplified using a suitable amplification technique. Zhang et al. is further directed to methods of detection involving hybridization signal amplification method and ramification extension amplification method.

As pointed out by the Examiner, Zhang et al. does not teach or suggest contacting amplicons with an array. See office action at page 10. Zhang et al. does not teach or suggest the amplification of ligation probes wherein the amplicons thus formed comprise adapter sequences. Nor does Zhang et al. teach or suggest hybridization of probes to a target, wherein the probes include the five portions outlined herein.

To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to

combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. In re Vaeck, 947 F2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Since neither Zhang nor Barany teach or suggest hybridization of probes to a target, wherein the probes include the five portions outlined herein, the requirement that the prior art reference (or references when combined) must teach or suggest all the claim limitations has not been met. Accordingly, Applicants respectfully request the Examiner to withdraw the rejection.

In addition, The Examiner states that it would have been obvious to one of ordinary skill in the art at the time the invention was made to have performed the method recited in claims 26 and 33 using a PCR product made by Zhang et al. as a hybridization probe in view of patents of Barany et al. and Zhang et al. The Examiner goes on to state that one of skill in the art would have been motivated to modify the method of Barany because simple replacement of one well known LDR/PCR method (Barany) with another well known LDR/PCR method (Zhang) in order to make a hybridization probe would have been in the absence of unexpected results, *prima facie* obvious. Applicants respectfully traverse.

In the instant case, there is lacking any motivation to modify or combine reference teachings. First of all contrary to the Examiner's characterization of Zhang as an LDR process like Barany, they operate in distinctly different ways. The LDR process of Barany uses hybridization probes directed to extension products (amplified products). In contrast, Zhang is directed to methods where the target is first captured through the use of capture probes and paramagnetic beads, then ligation occurs while still attached to the beads and after there is a release of the ligated amplification sequence from the beads, then there is amplification using a suitable PCR technique. See Zhang et al. at column 15, lines 35-41. If the proposed modification or combination of the prior art would change the principle operation of the prior art being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. In re Ratti, 270 F.2d 810, 123 USPQ 349 (CCPA 1959). Here the combination of the references would require substantial reconstruction and redesign of the elements shown in the primary reference (Zhang et al.) as well as a change in the basic principle under which Zhang et al. was designed to operate.

In addition, the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F 2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). For all of the foregoing reasons, the rejection is improper. Applicants respectfully request the withdrawal of the rejection.

Claims 9, 23 and 30 are rejected under 35 U.S.C § 103(a) as being unpatentable over Zhang et al., (1996) in view of Barany et al., (1997) as applied to claims 13, 19-22, 26, 31 and 33 above, and in further in view of Seradyn Particle Technology ("Seradyn") (November 1996).

Zhang et al. and Barany et al. have been discussed above and are incorporated at this point by reference.

The Examiner states that it would have been obvious to one of ordinary skill in the art at the time the invention was made to have removed non-hybridized probes using a method recited in claim 9 in view of the prior art of Barany et al., Zhang et al., and Seradyn Particle technology. The Examiner goes on to state that one of ordinary skill in the art would have been motivated to modify the method of Zhang et al. because

labeling different nucleic acids with a binding ligand was known in the art and simple replacement of one known nucleic acid separation method from another well known nucleic acid separation method during the process of determining the identification of a nucleotide at a detection position in a target sequence would have been, in the absence of unexpected results, *prima facie* obvious since using different methods to remove un-hybridized probes would not change the experimental results.

Applicants respectfully traverse.

As set forth above, Applicants note that Claims 9, 23 and 30 which form the bases for this rejection, are all dependent from claims 5, 26, 32 and 33. To this end, Applicants submit that neither Zhang nor Barany alone or in combination teach or suggest hybridization of probes to a target, wherein the probes include the five portions as outlined herein.

Furthermore, Seradyn fails to cure the deficiencies of Zhang or Barany or the combination of the two. Seradyn is directed to streptavidin magnetic microparticles for ligand binding. The particles are separated from suspension when a magnetic field is applied. Binding of ligands to streptavidin groups is accomplished using avidin-biotin technology. Seradyn does not teach or suggest methods for determining the identification of a nucleotide at a detection

position. Seradyn does not teach or suggest the use of upstream and downstream universal priming sites. In addition, Seradyn does not teach or suggest the hybridization of ligation probes to a target sequence, subsequent ligation of the ligation probes, amplification of the ligated probes, wherein the amplicons comprise adapter sequences, and contacting the amplicons thus formed with an array of capture probes. Finally Seradyn does not teach or suggest the use of arrays with capture probes.

The Examiner states that it would have been obvious to one of ordinary skill in the art at the time the invention was made to have removed non-hybridized probes using a method recited in claim 9 in view of the prior art of Barany et al., Zhang et al., and Seradyn Particle technology. The Examiner goes on to state that one of ordinary skill in the art would have been motivated to modify the method of Zhang et al. because labeling different nucleic acids with a binding ligand was known in the art and simple replacement of one known nucleic acid separation method from another well known nucleic acid separation method during the process of determining the identification of a nucleotide at a detection position in a target sequence would have been, in the absence of unexpected results, *prima facie* obvious since using different methods to remove un-hybridized probes would not change the experimental results. Applicants respectfully traverse.

The elements to establish a *prima facie* case of obvious is set forth above and is incorporated at this point by reference.

In addition, in determining the differences between the prior art and the claims, the question under 35 U.S.C § 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F2d. 1530, 218 USPQ 871 (Fed. Cir. 1983).

Claims 9, 23 and 30 which form the bases for this rejection, are all dependent from claims 5, 26, 32 and 33. Furthermore, none of the references alone or in combination teach or suggest hybridization of probes to a target, wherein the probes collectively include the five portions outlined herein. Therefore the requirement that the prior art reference (or references when combined) must teach or suggest all the claim limitations has not been met.

In addition, there is lacking any motivation of modifying or combining the reference teachings. The Examiner's statement that it would have been obvious to replace one known method of nucleic acid separation with another known method does not provide the specific guidance required to provide motivation to modify or combine the references of Zhang, Barany

and Seradyn to reach the claims of the present invention.

“Obvious to try” is not the standard and the very general statement that the Examiner points to that one known method can be simply replaced with another known method with modification of Barany does not provide specific guidance on how to reach the claims of the present invention.. It is improper to use an obvious to try approach or to cite to only general guidance as to the particular form of the claimed invention or how to achieve it. See *In re O’Farrell*, 853 F. 2d 894,903, 7 USPQ2d 1673,1681 (Fed. Cir. 1988). It is insufficient that the prior art disclosed the components of the patented invention, either separately or used in other combination; there must be some teaching, suggestion, or incentive to make the combination made by the inventor. *Northern Telecom, Inc. v. Datapoint Corp.*, 908 F.2d 931, 15 USPQ2d 1321 (Fed. Cir. 1990). The district court did not commit reversible error “by requiring that a claimed invention be “clearly suggested” by the prior art in order to be obvious. *Gillette Co. v. S.C. Johnson & Son, Inc.*, 919 F.2d 720, 16 USPQ2d 1923 (Fed. Cir. 1990).

Applicants submit that there is lacking any specific guidance as to a method of determining the nucleotide in a target sequence involving the amplification of ligated probes comprising the five portions outlined herein, formed through hybridization to target, wherein the amplicons thus formed comprise adapter sequences and then contacting the amplicons with an array of capture probes. In addition, there is lacking any suggestion in the references to modify the references or to combine them to reach the claims of the present invention. Therefore, the requirement that there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings has not been met. Accordingly, the rejection is improper and the Applicants respectfully request the withdrawal of the rejection.

In conclusion, the requirement that the prior art reference (or references when combined) must teach or suggest all the claim limitations has not been met. In addition, the requirement that there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings has not been met. Accordingly, the rejection is improper and Applicants respectfully request the withdrawal of the rejection.

CONCLUSION

Applicants submit that the claims are now in condition for allowance and early notification to that effect is respectfully requested. If the Examiner feels there are further unresolved issues, the Examiner is respectfully requested to phone the undersigned at (415) 781-1989.

Respectfully submitted,

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Dated: _____

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